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Cost of Hypoglycemia in Patients with Type 2 Diabetes in Sweden

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ABSTRACT

Objectives: Hypoglycemia is a common side effect of antidiabetic therapy. In addition to reducing well-being, hypoglycemic events may lead to substantial costs of medical care and lost productivity. The cost of hypoglycemia is, however, not well identified, particularly in patients with Type 2 diabetes. The purpose of this study was to assess the cost of hypoglycemia in Type 2 diabetes in Sweden.

Methods: A cost-of-illness approach, based on an incidence methodology, was used to estimate the cost of hypoglycemia in patients with Type 2 diabetes. A hypoglycemic event was defined as an episode with symptoms of low blood glucose levels during which the patient required assistance from another person. The events were divided into mild, moderate, and severe, and the incidence and costs of the different events were estimated based on data in the literature.

Results: Assuming that there are 300,000 patients with Type 2 diabetes in Sweden, it was estimated that 26,942 hypoglycemic events would occur annually in these patients, corresponding to a rate of 0.09 events per patient-year. The total cost of hypoglycemia was, in base case, estimated at about €4,250,000 (€14 per patient with Type 2 diabetes) per year. Moderate hypoglycemia contributed the largest proportion of these costs.

Conclusions: The results indicate that hypoglycemic events lead to substantial costs, but data are scarce and more studies are needed to better understand the cost and consequences of hypoglycemia.

Keywords: cost of illness, hypoglycemia, Sweden, Type 2 diabetes mellitus.

Introduction

In Sweden the prevalence of diabetes mellitus has been estimated to be about 3%, with Type 2 diabetes accounting for 85% to 90% of all diabetes cases [1]. The prevalence of Type 2 diabetes is increasing, mostly resulting from the aging population, but also resulting from changes in lifestyle factors (diet, exercise, smoking, etc.). By 2030, the World Health Organization predicts that diabetes will affect more than 370 million people worldwide [2]. Because diabetes is a major cause of morbidity and premature mortality, it has significant socioeconomic implications in both industrialized and developing nations, and the largest share of the costs is attributable to late complications of the disease (micro- and macroangiopathy) [1,3,4].

It is already well established that tight glycemic control reduces the development of diabetic complications [5,6]. Nevertheless, glycemic control is often forfeited to avoid treatment-related hypoglycemia, a common and feared side effect of insulin treatment [7]. The symptoms of hypoglycemia vary from very mild, for example, dizziness or headache, to severe symptoms requiring hospitalization. The prevalence of hypoglycemia varies depending on therapy options; in general, insulin therapy has been associated with the greatest incidence of hypoglycemia [8]. A large proportion of patients with Type 2 diabetes are treated with insulin [1], but hypoglycemia is less common in Type 2 versus Type 1 diabetes. Nevertheless, it is a cause for concern, and tends to be under-recognized [9]. Moreover, as physicians continue to move toward tighter glycemic controls in these patients, the incidence of hypoglycemia in Type 2 patients may increase in the future.

The cost of hypoglycemia is a complex issue as hypoglycemia affects the diabetic patient in multiple ways, and also because of the varying definitions of hypoglycemic events. Costs are incurred when healthcare resources are consumed to treat hypoglycemia (direct medical costs), and also because of loss in production when patients are absent from work (indirect costs). The direct medical costs in association with a hypoglycemic event depend on the severity of the event. Severe hypoglycemia may result in hospitalization, the moderate forms may need emergency care and consultation by a physician, and a mild hypoglycemic event may only require a glucagon injection or other assistance at the place of the event.

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Although the impact of hypoglycemia on quality of life (QoL) is unclear, patients experiencing several episodes of hypoglycemia have reported lower QoL [10]. Whether patients with low QoL experience many hypoglycemic events, or whether many hypoglycemic events lead to low QoL is, however, not known.

Apart from the distressing acute symptoms, hypoglycemia may also have a negative impact on the health of a patient with diabetes in the long term [11]. Another important aspect is the constant fear of developing hypoglycemia that some patients experience [12].

Few empirical studies have assessed the cost of hypoglycemia. Leese et al. estimated the cost of severe hypoglycemia to be about £380 per event [13] and a French study estimated the total hospital cost of a stay for hypoglycemia to FF14,000 (US$2100) [14]. A German study estimated the cost of severe hypoglycemia to US$44,338/100,000 inhabitants [15]. There is little data on the specific costs of hypoglycemia in Type 2 diabetes. The purpose of this study was therefore to assess the cost of hypoglycemia in Type 2 diabetes in Sweden.

Research Design and Methods

Method for Analysis of the Cost of Hypoglycemia

Cost-of-illness methodology was used to estimate the cost of hypoglycemia in patients with Type 2 diabetes in Sweden. The study design was incidence-based, considering all new events of hypoglycemia during a given year [16,17]. A bottom-up approach was used, with the costs of different hypoglycemic events being calculated and extrapolated to a national level, based on the estimated incidence rates of hypoglycemia. The calculation model is illustrated schematically in Figure 1.

Definition of Hypoglycemic Events

A hypoglycemic event was defined as an episode of hypoglycemia during which the patient required assistance from another person to resolve the situation (Table 1). A mild event required no medical attention and assistance from family or friends only. A moderate event required the help of medical personnel, typically a physician visit, but did not require admission to a hospital. A severe event was defined as a hypoglycemic episode requiring inpatient care. This definition of severe hypoglycemia differs from another definition often found in the literature, namely an event during which the patient requires assistance. This classic definition is not associated with resource use; therefore, the alternative definition was applied for the purposes of this analysis.

The definitions and reporting of rates of hypoglycemic events varies between studies in the literature. Many studies report the risk of having at least one event during a specified time period, whereas others report total number of events per patient per unit of time. As our summary estimates include studies that report the risk of having at least one event, there may be a slight underestimation of the total number of events as these patients may have experienced multiple events during the time period.

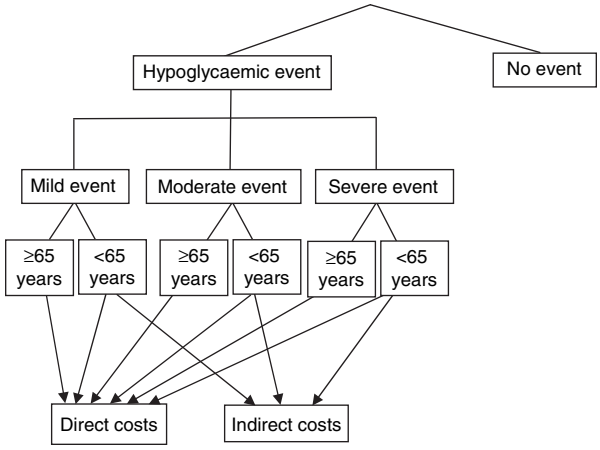

Figure 1 Model description.

Cost Calculations

Direct as well as indirect costs of hypoglycemia were considered. Direct costs included costs for the medical treatment of hypoglycemia, and indirect costs included productivity lost because of hypoglycemic events. When calculating the cost of lost productivity three basic assumptions were made: 1) a person experiencing a hypoglycemic event would not return to work that day; 2) if the event occurred at night, half a day of productivity would be lost; and 3) an event occurring after work but before sleep would result in no loss of productivity. Probabilities of a hypoglycemic event occurring at different times of the day were based on published data in patients with Type 1 diabetes [18]. There are no equivalent data available for patients with Type 2 diabetes; the analysis assumes that the diurnal patterns of hypoglycemia is comparable in Type 2 diabetes.

Table 1 Definition of hypoglycemic events

Hypoglycemia	Definition
Mild	Patient experiences symptoms of hypoglycemia and requires assistance from a second person (a relative or friend, etc.) to resolve the situation. No medical attention is needed
Moderate	Patient seeks medical attention for hypoglycemia but is not admitted to hospital overnight
Severe	Patient is admitted to hospital because of hypoglycemia

Intangible costs of hypoglycemia or effects on the QoL of patients were not included in the analysis because of a lack of published data.

All costs are estimated in a Swedish context and are presented in € 2005 value (1 € = 9.1 SEK [Swedish kronor]).

Results

Incidence of Hypoglycemia

The incidence of hypoglycemia was based on findings from several published studies, which are summarized in Table 2.

The incidence of hypoglycemia in patients using metformin treatment has been found to be very low and we therefore assumed for the purposes of this analysis that these patients have no hypoglycemic events. We assumed hypoglycemia incidence rates of 1.8% for patients using oral antidiabetic agents (OADs) other than metformin and 6.9% for patients using insulin. These assumed incidence rates were based on the results of the studies in Table 2. Nevertheless, these rates do not include very mild events that can be resolved without medical attention. To calculate the relative incidence of mild versus moderate and severe events, data from O'Brien et al. were used [19]. In this United States analysis the proportion of mild, moderate, and severe hypoglycemic events, according to the definitions used in the present study, was 71%, 28%, and 1%, respectively.

Swedish prescription statistics show that about 32% of the prescribed doses of OADs were for metformin. We therefore assumed that 68% of the patients on OADs will use drugs other than metformin, which means that we assume a hypoglycemia incidence rate among all OAD users of about 1.2%. Thus, the average incidence rate of all hypoglycemic events was estimated to be 0.042 and 0.24 events per patient-year for patients using OADs and insulin treatments, respectively.

Cost of Hypoglycemic Events

Mild hypoglycemia. It was assumed that patients who required assistance by another person but did not need medical attention would receive a glucagon injection at a price of €26.0 [20]. This was based on a previously estimated direct cost of a mild hypoglycemic event in patients with Type 1 diabetes [21]. Nordfeldt et al. [21] calculated the costs of hypoglycemic events in adolescents and children with Type 1 diabetes. Resource use was estimated from prospectively collected data of self-reported severe hypoglycemia in 129 patients below 19 years of age. Among other resource items, they included time that the parent had to spend away from work (i.e., lost productivity) to care for the child. In the case of adults with diabetes the production loss is twofold: that of the person experiencing the hypoglycemic event and that of the person providing assistance. Nordfeldt et al. [21] did not use the same distinction of severe events, but for the events that did not involve unconsciousness, 21 full days of production were lost to care for 95 events, equating to 0.22 days (1.76 h) lost per event. It is likely that caring for an adult patient would consume less time than caring for a child, however, in the case of an adult, both persons are likely to be part of the work force. With these two conflicting influences, the estimate should give equivalent actual time lost. Based on these data, the indirect cost of a mild hypoglycemic event was estimated to be €37.0, based on an average hourly wage rate, including benefits, and taxes (the labor cost for the employer), of €21.0 [22].

Moderate hypoglycemia. Costs were attributed to four possible outcomes for moderate hypoglycemia: visit to a general practitioner (GP); emergency room visit; home visit from the GP; or use of an ambulance; a possibility with emergency room visits. Unit costs for these, based on published data, were estimated at €129.7 for a GP visit [1], €343.4 for an emergency

Table 2 Data used to derived incidence of hypoglycemia

Study	Data available	Incidence of hypoglycemia
Miller et al. [8]	Incidence of hypoglycemia in patients with Type 2 diabetes by treatment type	Overall: 24.5% of patients over 8 months Insulin: 30% of patients over 8 months Oral: 16% of patients over 8 months Diet alone: 12% of patients over 8 months
Leese et al. [13]	Incidence of severe hypoglycemia requiring assistance of medical personnel	Insulin: 11.8 events/100 patients/year Sulfonylurea: 0.9 events/100 patients/year
	In patients with Type 2 diabetes by treatment type	Metformin: 0.05 events/100 patients/year
van Staa et al. [25]	Incidence of recorded hypoglycemic events	Sulfonylurea: 1.8% of patients per year
Holstein et al. [15]	Incidence of severe hypoglycemia in patients with Type 2 diabetes	Overall: 0.4% of patients per year
UKPDS [5]	Incidence of severe hypoglycemia in patients with Type 2 diabetes by treatment type	Insulin: 2.1–11.7% of patients per year Oral: 0–2.5% of patients per year
O'Brien et al. [19]	Proportion of mild, moderate, and severe hypoglycemic events	Mild: 71% of patients Moderate: 28% of patients Severe: 1% of patients

room visit [21], €233.3 for a GP home visit [1] and €185.3 for an ambulance [21]. Based on the resource utilization described in the diabetes control and complications trial (DCCT) [23], assuming that all events leading to hospitalization required the use of an ambulance, 9% of cases of moderate hypoglycemia will result in GP visits, 45% in emergency room visits, 45% in GP home visits and 33% the use of an ambulance. The weighted average costs and probabilities of each of the first three events were summed, and the costs of ambulance transportation added separately. This resulted in a total direct medical cost of €334.7 for each event of moderate hypoglycemia.

Indirect costs of moderate hypoglycemia were based on the assumptions that 16% of hypoglycemic events will occur between 08:00 and 13:00, 9% will occur between 13:00 and 18:00, 35% will occur between 18:00 and 00:00 and 40% will occur between 00:00 and 08:00 [18]. Hypoglycemia occurring at these times would result in the loss of 0.75, 0.25, 0, and 0.5 days of productivity, respectively. This equates to an average of 0.35 days lost per event. According to National Statistics, 77% of the population aged 18 to 65 years in Sweden are employed [22]. Applying this percentage to the current study, this would mean that 0.27 days (or 2.16 working hours) would be lost for each moderate event, translating to an indirect cost of €45.3.

Severe hypoglycemia. A study in France reported that 10,800 out of 40,000 events of severe hypoglycemia led to hospitalization [14]. The average length of stay in hospital was 6.6 days, at a cost of FF14,000 (at 1992 prices). This is similar to the average length of stay for patients hospitalized because of diabetes under the diagnosis-related groups (DRG) in Sweden, equating to an average cost of €2806.8 for each severe event leading to hospitalization [14]. In addition, the indirect cost of lost productivity from spending 6.6 days (52.8 h) in hospital would be €1110.6.

Table 3 Summary of the costs of hypoglycemic events (€ per event)

	Direct costs	Indirect costs	Total costs
Mild hypoglycemia	26.0	37.0	63.0
Moderate hypoglycemia	334.7	45.3	380.0
Severe hypoglycemia	2806.8	1110.6	3917.4

The total costs, both direct and indirect, of the different types of hypoglycemic events in Sweden are summarized in Table 3.

Total Costs of Hypoglycemia

Indirect costs will be incurred only in patients of a working age. Given that these costs form a relatively substantial portion of the total costs of hypoglycemia, we made the following assumption to estimate the share of patients with Type 2 diabetes who are of working age. According to Swedish prescription statistics during the year 2000, approximately 37% of prescribed OADs were for patients aged less than 65 years; therefore, we estimated that 37% of patients with Type 2 diabetes are of working age.

Assuming that there are 300,000 patients with Type 2 diabetes in Sweden [1,24], we would expect 26,942 hypoglycemic events to occur annually in these patients, corresponding to an average rate of 0.09 events per patient-year (Table 4).

From this base case assumption, the total cost of hypoglycemia in patients with Type 2 diabetes in Swe-

Table 4 Expected number of hypoglycemic events per year

	Insulin users aged ≤65 years	Insulin users aged >65 years	Oral treatment users aged ≤65 years	Oral treatment users aged >65 years	All Type 2 patients
Incidence (events per patient)	0.24	0.24	0.042	0.042	0.09
No. of patients in Sweden	33,300	56,700	47,064	80,136	300,000
No. of mild events	5,674	9,662	1,403	2,390	19,129
No. of moderate events	2,238	3,810	553	942	7,544
No. of severe events	80	136	20	34	269

Table 5 Expected yearly cost of hypoglycemic events

Cost	Insulin users aged ≤65 years	Insulin users aged >65 years	Oral treatment users aged ≤65 years	Oral treatment users aged >65 years	All Type 2 patients
Mild events (M€)	0.35	0.26	0.09	0.03	0.73
Moderate events (M€)	0.85	1.28	0.21	0.31	2.65
Severe events (M€)	0.31	0.39	0.08	0.10	0.87
Total (M€)	1.52	1.91	0.38	0.45	4.25
Per Type 2 patient (€)	45.7	33.7	8.0	5.6	14.1

M€, million €.

Table 6 Expected costs of hypoglycemic events for different incidence assumptions

Incidence (events per patient and year)*		Base case distribution assumption†		Distribution assumption 2‡		Distribution assumption 3§	
Insulin users	OAD users	Total cost per year (M€)	Cost per Type 2 patient (€)	Total cost per year (M€)	Cost per Type 2 patient (€)	Total cost per year (M€)	Cost per Type 2 patient (€)
0.048	0.0084	0.8	2.7	0.5	1.7	1.3	4.3
0.120	0.0210	2.0	6.7	1.3	4.3	3.2	10.6
0.192	0.0336	3.2	10.7	2.1	6.9	5.1	17.0
0.288	0.0504	4.8	16.0	3.1	10.3	7.7	25.5
0.360	0.0630	6.0	20.0	3.9	12.9	9.6	31.9
0.480	0.0840	8.0	26.7	5.1	17.2	12.8	42.6
0.720	0.1260	12.0	40.1	7.7	25.7	19.2	63.9

*Base case estimate: 0.24 for insulin users and 0.042 for oral treatments users.
†Base case assumption: proportion of mild, moderate, and severe hypoglycemic events: 71%, 28%, and 1%.
‡Distribution assumption 2: proportion of mild, moderate, and severe hypoglycemic events: 85%, 14.5%, and 0.5%.
§Distribution assumption 3: proportion of mild, moderate, and severe hypoglycemic events: 60%, 37%, and 3%.
M€, million €.

den was estimated to be approximately €4,250,000 (€14.1 per patient with Type 2 diabetes). Moderate hypoglycemia contributed the largest proportion of these costs (Table 5).

Given that the incidence estimates used to derive these costs are uncertain, the impact of differing event rates and proportion of mild, moderate, and severe events on cost estimates were evaluated (Table 6).

Discussion

Hypoglycemia is common in patients with diabetes, although the incidence of different degrees of hypoglycemia remains uncertain. This study estimated that patients with Type 2 diabetes would on average experience about 0.09 hypoglycemic events per year, which translates into 27,000 events annually in Sweden at a total cost of €4 million, or €14 per patient with Type 2 diabetes. Moderate hypoglycemic events were the largest contribution to the total cost. The risk of hypoglycemic events may be slightly underestimated, because it is partly based on studies reporting the risk of patients experiencing at least one event rather than the total number of events.

The calculated cost did not include the intangible cost of hypoglycemic events or of the fear of developing hypoglycemia. Mortality associated with hypoglycemia was also excluded; a mortality rate of approximately 0.04% has been reported for mild and moderate hypoglycemic events, and the mortality after a severe event (hospitalization) has been estimated at 1.9% [14,21]. Another possibly important effect of a reduction in the risk of hypoglycemia is an improvement in glycemic control, which may lead to a reduced risk of macrovascular complications. The consequences of this in terms of costs and well-being are, however, difficult to assess, but could possible be even more important than the short-term consequences of hypoglycemia. Given that these factors were not included, the costs associated with hypoglycemia in patients with Type 2 diabetes may be even higher than those reported here.

In conclusion, the results of this analysis show that hypoglycemic events in patients with Type 2 diabetes are associated with substantial costs. Data regarding this treatment-related side effect are, however, scarce and more studies are needed to better understand the cost and consequences of hypoglycemia. Incidence and resource use for hypoglycemia, in particular for mild hypoglycemia are therefore important areas for further research. The effects of hypoglycemia on QoL and the willingness to pay for avoiding hypoglycemic events are also interesting subjects for future study.

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